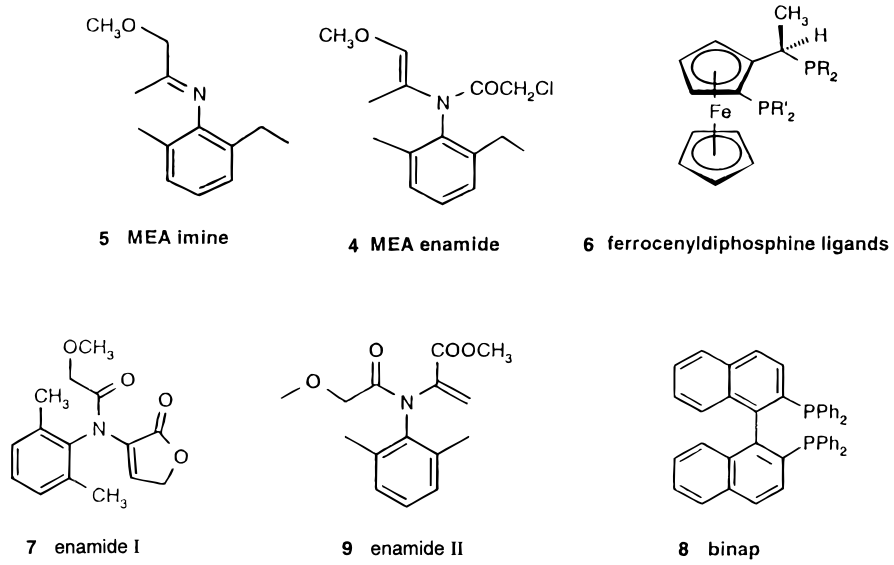

Fig. 3. Structures of intermediates and catalysts mentioned in text.

hydrogenation of the enamide II (Fig. 3, **9**). Of 34 chiral Rh diphosphine catalysts tested, 12 produced ees >90% but most showed low activity. Optimization and scale-up experiments were done with the catalyst $[Rh(nbd)_2]BF_4$/(R,R)-Me-duphos. With hydrogen at 10 bar and 60°C, and with a substrate-to-catalyst ratio of 5×10^4, 95·6% ee and a turnover frequency of $5{\cdot}2 \times 10^3\ h^{-1}$ were obtained, well above the specified minimum limits. The alternative route via enantioselective hydrogenation of the corresponding imine turned out not to be feasible.

Acknowledgements
The summarized results are due to the efforts of several teams of very dedicated chemists, engineers and technicians and we would like to acknowledge the contributions of R. Hanreich, H.-D. Schneider, A. Togni, A. Wirth-Tijani, M. Fischer, R. Häusel, H. Landert, S. Maurer, M. Parak, G. Thoma and N. Vostenka. We also thank Rolf Bader, Beat Böhner, John Dingwall and Gerardo Ramos for their continuous encouragement and support.

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Synthesis and Insecticidal Evaluation of Imidacloprid Analogs

Jérome Boëlle,[1] Raphaël Schneider,[1] Philippe Gérardin,[1] Bernard Loubinoux,[1]* Peter Maienfisch[2] & Alfred Rindlisbacher[2]

[1] LERMAB, Laboratoire de Chimie Organique et Microbiologie, Université Henri Poincaré, Nancy I. Faculté des Sciences, BP 239, 54506 Vandoeuvre-lès-Nancy Cedex, France
[2] Novartis Crop Protection AG, CH-4002 Basel, Switzerland

Abstract: Imidacloprid analogues containing a nitroalkylidene instead of a nitroguanidine unit have been prepared and evaluated for investigation as potential insecticides. No nitroalkylidene analogue showed significant activity against the test insects. © 1998 Society of Chemical Industry

Pestic. Sci., **54**, 000–000 (1998)

Key words: imidacloprid; insecticide; α-nitroalkene

1 Introduction

Imidacloprid (Fig. 1; **1**) is a systemic neonicotinoid[1] insecticide discovered by Bayer.[2] It controls a broad range of commercially important pests such as soil and sucking insects and termites and is used as seed dressing, as a soil treatment and as a foliar treatment in such

* To whom correspondence should be addressed.
E-mail: Bernard.Loubinoux@lermab.u-nancy.fr

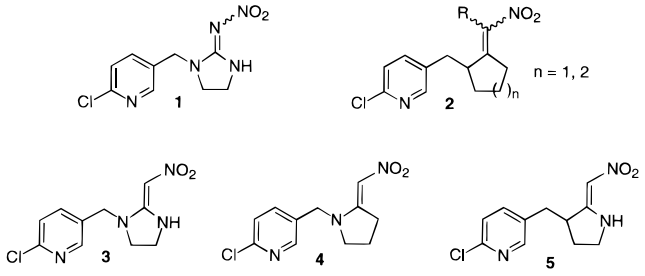

Fig. 1. Structures of compounds discussed in text.

crops as cotton, cereals, maize, rice, vegetables and potatoes.[3]

Structure–activity relationships of imidacloprid (**1**) have been studied extensively. Tomizawa and Yamamoto[4] reported good insecticidal activity for compounds **3** and **4** and demonstrated that replacement of the nitroguanidine group in **1** by a nitroenamine group retains activity. In addition, Maienfisch *et al.*[5,6] reported that compound **5**, a regio isomer of **4**, possesses similar insecticidal activity to that of imidacloprid.

In this summary we describe the synthesis and biological evaluation of new analogues of these compounds containing a nitroalkylidene unit instead of the nitroguanidine or nitroenamine unit, respectively. (Fig. 1, **2**).

2 *Materials and methods*

2.1 Synthesis of compounds. The preparation of compounds of structure **2** is outlined in Fig. 2. 2-(2-Chloropyrid-5-ylmethylcycloalkanones **8** were easily prepared by addition of 2-chloro-5-chloromethylpyridine to the sodium enolate of ketoester **6**, followed by hydrolysis and decarboxylation of **7**. Reaction of dilithiodinitronates with **8** afforded nitroalkanols **9** in good yields. Conversion of tertiary β-nitroalcohols **9** into **2** was the key step of the synthesis. Indeed, the use of methods described in the literature for dehydration of β-nitroalcohols, generally secondary alcohols, failed and prompted us to investigate another method.[7] We found that rapid and clean conversion of **9** into **2** could be performed by acylation of **9** followed by acetic acid elimination with potassium *tert*-butoxide or potassium methoxide according to the nature of R^1.

2.1.1 Preparation of ethyl 1-(2-chloropyrid-5-ylmethyl-2-oxocycloalkane carboxylate (**7**). Ketoester **6** (20 mmol, $n = 1$ or 2) in anhydrous THF (10 ml) was added dropwise at 0°C to sodium hydride (22 mmol) in anhydrous THF (30 ml) under a nitrogen atmosphere. The mixture was stirred for 30 min at 25°C, a solution of 2-chloro-5-chloromethylpyridine (22 mmol) in THF (20 ml) was then added dropwise and the resulting mixture refluxed for 24 h, cooled to room temperature, poured into water (200 ml) and extracted with ether (2 × 75 ml). The combined organic layers were dried (magnesium sulfate), filtered and the solvent removed under reduced pressure. The residue was chromatographed on silica gel with hexane + ethyl acetate (92 + 8 by volume) as eluent.

2.1.2 Preparation of 2-(2-chloropyrid-5-methylcycloalkanones (**8**). Product **7** (10 mmol) was refluxed in concentrated hydrochloric acid (10 M; 18 ml) until disappearance of starting material (monitored by TLC). The cooled mixture was extracted with ether (2 × 50 ml), the combined organic layers washed with $NaHCO_3$ solution (50 g litre^{-1}; 50 ml), then with water (50 ml) and finally dried over magnesium sulfate. The solvent was removed under reduced pressure to leave an oil which was used without purification in the next step.

2.1.3 Preparation of 2-(2-chloropyrid-5-ylmethyl-1-nitroalkylcycloalkanols (**9**). To a solution of dilithionitronate, prepared according to Seebach's procedure[8]

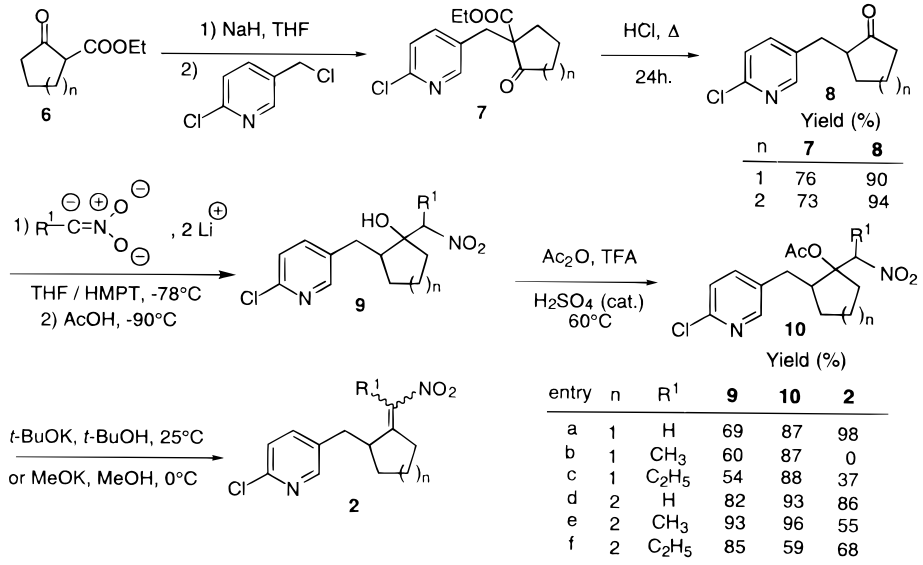

Fig. 2. Synthesis of imidacloprid analogues **2**.

TABLE 1
Insecticidal Activity of Nitroalkylidenes **2** and Reference Compounds

Pest	Stage[b]	Concentration (mg AI litre^{-1})	Insecticidal activity[a]							
			1	*3*	*4*	*5*	*2a*	*2d*	*2e*	*2f*
Spodoptera littoralis	L1	100	++	++	++	++	−	−	−	−
Diabrotica balteata	L3	100	++	++	++	++	−	−	−	−
Aphis craccivora	m.p.	100	++	++	++	++	−	−	−	−
Myzus persicae	m.p.	12·5	++	++	++	++	−	−	−	−
Nilaparvata lugens	N3	100	++	++	++	++	−	−	−	−

[a] ++ >80% mortality; − <30% mortality.
[b] L1: first-instar larvae, L3: third-instar larvae, m.p.: mixed population, N3: third-instar nymph.

from nitroalkane (10 mmol) and *n*-BuLi (20 mmol, 12·5 ml, 1·6 M in hexane) in THF + HMPT (5 + 1 by volume), a solution of ketone **8** (5 mmol) in THF (5 ml) was added dropwise at −70°C, and the mixture kept at −70°C for 3 h. Acetic acid (3 ml) in THF (4 ml) was then added. The resulting mixture was warmed to room temperature, poured into water (80 ml) and extracted with ether (2 × 100 ml). The combined organic layers were washed with water, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel with hexane + ethyl acetate (92 + 8 by volume) as eluant.

2.1.4 Preparation of 2-(2-chloropyrid-5-methyl)-1-nitroalkylcycloalkyl acetates (**10**). β-Nitroalcohol **9** (7 mmol), acetic anhydride (8·4 mmol), trifluoroacetic acid (8·4 mmol) and concentrated sulfuric acid (1 drop) were mixed and reacted at 60°C until disappearance of starting material (monitored by TLC). After cooling, ether (100 ml) and water (25 ml) were added. The organic layer was separated, washed with $NaHCO_3$ solution (50 g litre^{-1}; 25 ml) and brine (25 ml) and then dried over magnesium sulfate. Removal of the solvent gave **10** as a yellow oil.

2.1.5. Preparation of 2-(2-chloropyrid-5-ylmethyl)-1-(2-nitroalkylidene)cycloalkanes (**2**). To a solution of β-nitroacetate (**10a** or **10d**; 3 mmol) in methanol (10 ml) potassium methoxide (3 mmol) in methanol (5 ml) was added dropwise at 0°C. The mixture was stirred at 0°C until the disappearance of the starting material (monitored by TLC). Ether (100 ml) and water (50 ml) were then added, the organic layer was separated, dried over magnesium sulfate and concentrated to give **2**.

The same procedure was used for the synthesis of trisubstituted α-nitroalkenes **2c**, **2e** and **2f** with *tert*-BuOK/*tert*-BuOH instead of MeOK/MeOH.

2.2 Insecticidal tests. 2.2.1 *Feeding-contact activity.* Test units, each containing pea seedlings, potted rice seedlings, sprouted corn seeds and cotton leaf discs, were sprayed in a spray chamber at *c.* 500 litre ha^{-1} with the test compound dissolved in a standard mixture of organic solvents and diluted in water to 100 mg active ingredient litre^{-1}.

Pea seedlings were infested with a mixed population of *Aphis craccivora* Koch (groundnut aphid) prior to the application (curative spray). The other test plants were infested after the application (preventive spray). Sprouted corn seeds received 10 third-instar larvae of *Diabrotica balteata* Le Conte (banded cucumber beetle); rice seedlings 20 third-instar nymphs of *Nilaparvata lugens* Staol (brown plant hopper) and cotton leaf discs 20 first-instar larvae of *Spodoptera littoralis* Boisd. (Egyptian cotton leafworm). The test units were held at 25°C and 50% relative humidity and the percentage mortality evaluated after five days.

2.2.2 Systemic activity. Pea seedlings, infested with a mixed population of *Myzus persicae* Sulz (green peach aphid) were placed directly in the test solution (12·5 mg AI litre^{-1}) prepared following the same procedure as used for the feeding-contact test. The test units were held at 22°C and 50% relative humidity and the percentage mortality evaluated after five days.

3 *Results and discussion*

Table 1 shows the insecticidal test results of a series of the nitroalkylidenes **2** in comparison to imidacloprid (**1**), its nitroenamine analogue **3** and the nitromethylene pyrrolidines **4** and **5**. In contrast to the reference compounds **1**, **3**, **4** and **5**, all compounds **2** tested showed little insecticidal activity against *S. littoralis*, *D. balteata*, *A. craccivora*, *M. persicae* and *N. lugens* at 100 mg litre^{-1} (12·5 mg litre^{-1} for *M. persicae*). From these data it can be concluded that the replacement of the nitroguanidine or nitroenamine group by a nitroalkylidene group is responsible for this loss in insecticidal activity, probably due to the marked change in the electrostatic properties of the compounds.[9]

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Synthesis and Insecticidal Evaluation of *N*-Substituted 2-Nitroiminoimidazolidines

Jérome Boëlle, Raphaël Schneider, Philippe Gérardin & Bernard Loubinoux*

LERMAB, Laboratoire de Chimie Organique et Microbiologie, Université Henri Poincaré, Nancy I. Faculté des Sciences, BP 239, 54506 Vandoeuvre-lès-Nancy Cedex, France

Abstract: *N*-substituted and *N*,*N*′-disubstituted 2-nitroiminoimidazolidines were prepared from 2-nitroiminoimidazoline. The feeding-contact and systemic activities as insecticides of some of these new compounds have been evaluated. © 1998 Society of Chemical Industry

Pestic. Sci., **54**, 000–000 (1998)

Key words: imidacloprid; insecticide; *N*-substituted 2-nitroiminoimidazolidines

1 Introduction

Imidacloprid (Fig. 1: IMI, **1**), which acts on diverse acetylcholine receptors (nAChR) of insect origin, is a relatively new, selective, long-acting neonicotinoid insecticide which can be used with reasonable environmental safety.[1,2] It shows excellent field efficacy even towards insects resistant to the conventional insecticides and is widely used for controlling pests on rice, vegetables and fruit trees.[3]

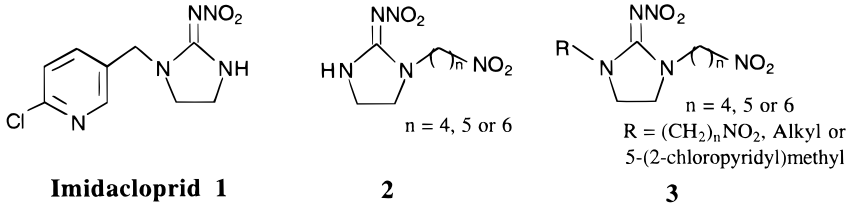
In this paper, structural modification on the 2-nitroiminoimidazolidine ring are reported and insecticidal properties of some of the new compounds (Fig. 1; **2**, **3**) evaluated.

2 Materials and Methods

2.1 Synthesis of compounds. The synthesis of *N*-substituted and symmetrically *N*,*N*′-disubstituted compounds with structures **2** and **3** was achieved as shown in Fig. 2. Compound **4**, prepared in 58% yield from nitroguanidine and ethylene diamine,[4] could be mono- or dialkylated with halogeno derivatives in acetonitrile under reflux to give **5** and **6**, respectively, in good yields. The attack of two 2-nitroiminoimidazolidine units on the same halogeno derivative could be avoided by using an excess of the latter (2·2 eq. for *N*-monoalkylation, 4·0 eq. for *N*,*N*′-dialkylation). Subsequent treatment of **5** and **6** with silver nitrite in ether containing a few drops of dichloromethane afforded **2** and **3** in good yields.

Unsymmetrical *N*,*N*′-disubstituted compounds **8** and **9** were prepared using a similar methodology (Fig. 3). Each alkylation step was performed with 1·1 eq. of halogeno derivative. Nucleophilic substitution of the

* To whom correspondence should be addressed.
E-mail: Bernard.Loubinoux@lermab.u-nancy.fr



Imidacloprid 1 **2** **3**

Fig. 1. Structures of compounds discussed in text.

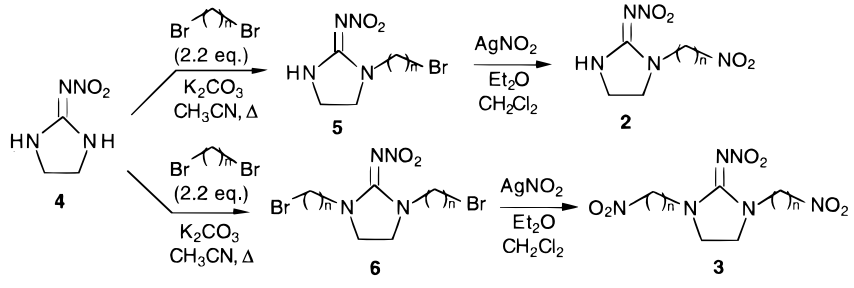


Fig. 2. Synthesis of *N*-substituted and symmetrical *N*,*N*′-disubstituted 2-nitroiminoimidazolidines.